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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/473,872	12/28/99	YOON K	JEFF-Y0001

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EXAMINER	
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ART UNIT	**PAPER NUMBER**
1632	12

DATE MAILED: 03/21/01

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.	Applicant(s)
09/473,872	Yoon
Examiner	**Group Art Unit**
Peter Brunovskis	1632

☒ Responsive to communication(s) filed on *Jan 3, 2001*

☒ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *3* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claim

☒ Claim(s) *1-40* is/are pending in the applicat

Of the above, claim(s) _____ is/are withdrawn from consideration

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *1-40* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☒ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

The response filed 1/08/00 has been entered. Amendment of claims 1, 4, 8-10, 18, 19, 23-25, and 32-40 is acknowledged. Claims 1-40 are pending in the instant application. Applicant's arguments filed 1/03/00 will only be considered or addressed to the extent that they apply to the *pending claims*; unless otherwise indicated, arguments directed to rejections that are rendered moot in view of Applicants amendments will not be further addressed.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-17 and 23-25 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 (and dependent claims) is indefinite in its recitation of the phrase "...at said locations of the human skin wherein the chimeric RNA-DNA oligonucleotide has a double hairpin structure with pyrimidine loops" since it is unclear whether the resultant phenotypic changes only occur in locations where the RNA-DNA oligonucleotide has a double hairpin structure with pyrimidine loops or whether the changes occur in locations whereto the RNA-DNA

oligonucleotide has been delivered. Changing the claim to --...composition sufficient to bring about stable genetic and phenotypic modifications in the selected gene at said locations wherein the compositions comprises a chimeric RNA-DNA oligonucleotide having a double hairpin structure with pyrimidine loops and a pharmaceutically effective carrier.-- (or equivalent) would obviate the rejection.

Claims 8-10 and 23-25 are indefinite in their recitation of the phrase "contiguous nucleotides in each of the first and second strings" since it is unclear whether the "contiguous" is directed to the structural relationship existing between the first and second strings or whether it merely recites the fact that each of the two strings contain a set of contiguous nucleotides, which may or may not be contiguous with those of the other string(s).

Claims 8-10 and 23-25 are indefinite in their recitation of "nuclease protected"since it is unclear how this term is defined, what metes and bounds apply, or how the limitation applies to the nucleotides in loops that would appear *susceptible* to nucleases.. Further, it is unclear whether the first and second strings are contiguous.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 2-4, 19, 32, and 33 remain rejected under 35 U.S.C. 112, first paragraph, for the reasons of record set forth in the Office Action of 6/21/00 and for the reasons set forth below as

containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Applicant's arguments filed 1/03/01 have been fully considered but they are not persuasive. The response contends that the claimed subject matter does not embrace claims to gene sequences recited in claims 4, 19, and 33 and asserts that "the specification provides scientific journal article citations to these genes as listed in Table 1 on pages 51 and 52 of the specification" which are incorporated by reference and which are available in the public databases (paragraph abridging p. 15-16). This argument is not persuasive because the rejected claims recite or embrace genes or as yet undiscovered skin disorders that are not adequately described in a manner commensurate with the claimed subject matter. For example, the response contends that GenBank accession number 6678659 provides the gene sequence for LAMA3. However, the sequence disclosed in GenBank accession number 6678659 is drawn to a mouse sequence, despite the claims embracing methods for modifying genes in human skin. Further, many of the cited references in Table 1 are review articles which do not report any of the essential sequences necessary for designing chimeric RNA-DNA oligonucleotides commensurate with the claimed methods. Moreover, the rejected claims broadly embrace methods for introducing genetic and phenotypic modification in human skin comprising yet to-be-discovered skin disorders lacking a known genetic basis at the present time. Consequently, the generic claims do not fully describe the genus of disorders commensurate with the breadth of the claimed subject matter.

Claims 1-40 remain rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods for creating stable genetic modifications in the skin of mice comprising genetic and phenotypic alteration in mouse tyrosinase, COL7A1, and KRT17 genes *using specific RDOs disclosed in the working examples*, does not reasonably provide enablement for methods for making and using stable genetic modifications in the skin of humans and other animals comprising genetic and phenotypic alterations involving the broad scope of genes recited in the claims. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Applicant's arguments filed 1/03/01 have been fully considered but they are not persuasive. In response to the Examiner's position that the disclosure does reveal the specific types of RDO substrates or structures that are amenable for in vivo genetic modification in skin or whether any of the working examples support the notion that insertions or deletions can be similarly introduced in skin (as point mutations), Applicants submit that "compliance with 35 U.S.C. 112, first paragraph, does not turn on whether an example is disclosed. MPEP 2164.02....and that "[t]o satisfy the enablement requirement, Applicant need not describe all actual embodiments" (p. 17). However, MPEP 2164.02 also states that "[l]ack of a working example, however, is a factor to be considered, especially in a case involving an unpredictable and undeveloped art".

Importantly, the Office Action of 6/21/00 clearly establishes that the subject invention is drawn to a highly unpredictable and undeveloped art. As noted in the Office Action of 6/21/00,

Stephenson recently reported that "many laboratories have been unsuccessful in getting the technique [i.e. RDO methodology] to work or have achieved only modest rates of gene conversion (JAMA, vol. 281(2), Jan. 13, 1999, p. 120), while Michael Strauss, a skilled artisan, reported that "[m]any researchers (including our group) have since applied this technology to their gene of interest and most of them have failed so far" (Nature Med. vol. 4, March 1998, p. 275, middle of left column). Strauss goes on to say that "[t]he paper by Kren et al. is both very inspiring and very controversial. It should be regarded as the initial venture into developing molecular tools for site-specific correction of certain gene rather than as a complete kit for the correction of all genetic defects" (p. 275, bottom paragraph, middle column). The inability of multiple groups to duplicate the results of just one or two laboratories suggests the need for a better understanding of the mechanism involved in this process, but more importantly, the key RDO structures and method steps that would enable one of skill in the art to practice this technology as broadly as is claimed. Applicant has previously stated in the prior art that "it's not clear why the efficiency of the procedure, using the same cells and the same chimeric molecule, varies so widely (Stephenson, JAMA, 281(2), p. 120, left column, last paragraph). Moreover, as quoted in Stephenson, Applicant Yoon states that: "[b]ecause factors such as recombination frequency, cell cycle, and other elements vary among cell types, it may not be possible to apply the technology to all cells (p. 120, middle column, top paragraph). These observations underscore the need for working examples to enable the broad scope of claimed subject matter in this highly unpredictable and undeveloped art, particularly since it is not readily apparent from the

specification what critical features are responsible for the limited success observed in the narrow context of mice whose skin was shown to be genetically modified by site-specific nucleotide substitution--not insertion or deletion. The response fails to address these failures in the art by others or the lack of understanding concerning the mechanism involved in this process so as to enable the broadly claimed subject matter beyond the limited working examples presented in the instant specification.

The fact that the cited references do not concern modification of genes in human skin in vivo does not mitigate the issue of unpredictability in the instant case, as suggested by Applicants (p. 17), since Applicants have failed to provide a sufficient explanation as to why Applicants approach has not been shown to reproducibly work in other laboratories. Applicants appear to suggest that their success can be ascribed to the fact that skin comprises rapidly renewing tissues in a process of constant regeneration which presumably allows for an apparent high level of gene conversion following epidermal stem cell gene modifications. However, this explanation appears to be at odds with the Applicants observation concerning a high frequency of gene modification achieved in vivo in contrast to that in vitro; cells cultured in vitro would be expected to more closely resemble, at a metabolical level, the presumed RDO target cells of the instant invention (epidermal stem cells) in contrast to the predominant cell type in skin that is quiescent, nondividing, and postmitotic. The fact that Applicants have not adequately resolved the question of why their method works so well in vivo in contrast to in vitro underscores the lack of predictability in this undeveloped art. Applicants have not provided any cogent argument as to

why their disclosure is broadly enabled for genetic modifications involving insertions and deletions, given the paucity of data showing that this is even possible in cells, let alone skin cells in vivo.

Applicants further contend and/or speculate that due to similarities between human and mouse skin cell types, "gene modifications and phenotypic changes obtained with the mouse system can also be achieved in humans because of similarity of cell types in mosue and human" (p. 18). These general statements, along with the assertion that "mouse skin provides a valuable animal model for human skin diseases" do not provide a sufficient nexus for concluding that the claimed methods, as recited in the mouse models, can be readily extrapolated to humans. For example, Crystal has previously noted that "[h]umans are not simply large mice. There have been several surprise examples, in which predictions from gene transfer studies in experimental animals have not been borne out in human safety and efficacy trials" (Science, 270:404-410, 1995; p. 409, bottom, left column).

The response further fails to address the insufficient guidance concerning the threshold levels of correction required to generate a phenotypic change or to constitute a measurable phenotypic change within the context of the broad range of genetic disorders recited. With respect to enabling the broad scope of embodiments covered by the instant claims, Applicants are referred to the "germ of an idea" concept defined by the CAFC. The court has stated that "patent protection is granted in return for an enabling disclosure, not for vague intimations of general ideas that may or may not be workable". The court continues to say that "tossing out the

mere germ of an idea does not constitute an enabling disclosure" and that "the specification, not knowledge in the art, must supply the novel aspects of an invention in order to constitute adequate enablement". (See *Genentech inc v. Novo Nordisk A/S* 42 USPQ2d 1001, at 1005). As broadly claimed, the compositions and methods of the claimed invention constitute such a "germ of an idea". In view of the unpredictability and undeveloped state of the art as described above, it would likely require undue experimentation for one skilled in the art to appropriately develop the claimed invention for genetic modification in accordance with the broad scope of the claimed subject matter.

No claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event,

however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Certain papers related to this application may be submitted to Art Unit 1632 by facsimile transmission. The FAX number is (703) 308-4242 or 305-3014. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 CFR 1.6(d)). NOTE: If applicant *does* submit a paper by FAX, the original copy should be retained by applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED, so as to avoid the processing of duplicate papers in the Office.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Peter Brunovskis whose telephone number is (703) 305-2471. The examiner can normally be reached on Monday through Friday from 8:30 AM to 5 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Karen Hauda can be reached at (703) 305-6608.

Any inquiry of a general nature or relating to the status of this application should be directed to the Patent Analyst, Patsy Zimmerman whose telephone number is (703) 308-8338.

Peter Brunovskis, Ph.D.
Patent Examiner
Art Unit 1632

Scott D. Priebe

SCOTT D. PRIEBE, PH.D
PRIMARY EXAMINER